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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/786,481	03/05/2001	Frank Hulstaert	11362.0034.P	8708

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EXAMINER	
NICHOLS, CHRISTOPHER J	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 12/16/2002 7

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/786,481	HULSTAERT ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 14-17* is/are pending in the application.

4a) Of the above claim(s) *4 and 14-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-11 and 14-17* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 March 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election **with** traverse of Group I (Claims 1-3 and 5-11) drawn to a method for early in vitro detection and/or quantification of central nervous system (CNS) damage in an individual wherein the sample is taken from the cerebrospinal fluid of an individual in Paper No. 6 (15 October 2002) is acknowledged. The traversal is on the ground(s) that current amendment of the claims as restricted voids the prior art (WO 94/13795) used to establish lack of unity in Paper No. 4 (12 September 2002). This is not found persuasive because the CNS damage described in WO 94/13795 is due to Alzheimer's disease (AD). In AD, neurotoxic plaques of insoluble protein form in the brain, these plaques, as compositions of matter, read on the limitation of "a physical agent" in the Amended claim #1. Claims 4 and 14-17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 1-3 and 5-11 will be examined to the extent that they read on a method for early in vitro detection and/or quantification of CNS damage in an individual wherein the sample is taken from the cerebrospinal fluid (CSF) of an individual

Status of Application, Amendments, and/or Claims

2. The Preliminary Amendments Paper No. 5 (15 October 2002), Paper No. 6 (15 October 2002), Paper No. 3 (5 March 2001) have been received and entered in full.

3. Claims 4 and 14-17 are withdrawn from consideration as discussed above, claims 12 and 13 are cancelled, and claims 1-3 and 5-11 are under examination.

4. To aid in correlating any papers for this application, all correspondence regarding this application should be directed to Art Unit 1647, Examiner Christopher Nichols.

Priority

5. The effective US filing date for this application (09/786481) is 7 September 1999. Acknowledgment is made of applicant's claim for foreign priority based on PCT/EP99/06592. The priority date for this application (09/786481) is 7 September 1998 based on PCT/EP99/06592.

Information Disclosure Statement

6. The information disclosure statement filed 5 March 2001 (Paper No. 3) fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because Tranchant (1997) is not in the English language. It has been placed in the application file, but the citation(s) listed above have not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

Oath/Declaration

7. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: the Oath/Declaration contains non-initialed hand written correction. Appropriate correction is required.

Drawings

8. The drawings are objected to because the lines corresponding to the "15" and "18" data sets in Figure 2 are not clearly drawn. In addition, the figure legend for Figure 2 is not decipherable. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-3 and 5-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 1 is directed to a method for early detection and/or quantification of CNS

damage in an individual. Claim 2 is directed to a method for the early *in vitro* detection and/or quantification of CNS damage in an individual. Claim 3 is directed to the method according to claim 2 in which the sample is taken from the cerebrospinal fluid of the individual. Claim 5 is directed to the method according to claims 1 or 2 in which the CNS damage is caused by a benign primary brain tumor, a malignant primary brain tumor, a brain metastasis, or a subdural hematoma. Claim 6 is directed to the method according to claims 1 or 2 in which the invasion or metastasis of the CNS is by leukemia, lymphoma, or breast cancer. Claim 7 is directed to the method according to claims 1 or 2 in which the organisms are bacteria or viruses causing encephalitis or meningitis. Claim 8 is directed to the method according to claims 1 or 2 in which the anoxia or ischemia is caused by stroke. Claim 9 is directed to the method according to claims 1 or 2 in which the chemical agent is gene therapy, pharmaceuticals, chemotherapy, or exposure to chemical compounds. Claim 10 is directed to the method according to claims 1 or 2 in which the physical agent is a trauma, stroke, intracranial pressure, or radiation. Claim 11 is directed to the method according to claims 1 or 2 in which CNS damage is detected and/or quantified in order to evaluate the effect of a certain treatment on said CNS damage.

10. The specification teaches that under normal circumstances, the adult human brain contains 2-3 mol phosphate per mole of tau. Phosphorylation of different sites in normal tau as studied in rat and humans is dependent on the developmental state. Tau variants of 60, 64, and 68 kDa, due to phosphorylation, have been detected in brain areas with neurofibrillary tangles. These brains contain 6-8 mol phosphate per mol tau. In tau isolated from paired helical filaments, phosphorylation can occur at several positions. Detection of normally and abnormally phosphorylated tau in brain extracts is done either via antibodies, via the change in molecular

weight, or else by functional assay. A combination of monoclonal antibodies, each recognizing specific epitopes of tau, has been used to detect the presence of normally and abnormally phosphorylated tau in CSF (cerebrospinal fluid). Tau has been used as a marker to discriminate dementia with altered cytoskeletal properties such as Alzheimer's disease from normal aged subjects or from patients with other types of dementia.

11. The art teaches that tau is a structural protein in neurons and its abnormally phosphorylated form is the major building block of the paired helical filament structure (PHF) comprising neurofibrillary tangles (NFT) in Alzheimer's disease (AD). Tau is present in high levels in neurons and serves to stabilize the microtubule network in axons (Gotz, 2001). Tau in the CSF is the most widely studied biomarker for AD. The low levels of tau in CSF can be measured using ELISAs. CSF tau does not show a cranial-caudal reproducibility. Concentration gradient, and levels of tau are unaffected by time of day. Several studies, using ELISAs that detect all forms of tau (total tau) have reported increased levels of CSF tau in AD compared to controls. Pooling data across studies in not straightforward, because of varying patient populations and control, and technical factors related to ELISA assay. In larger studies, about 65-90% of AD patients show increased CSF tau. Tau levels are elevated in early stages of AD and do not correlate with age, gender, or age of dementia onset, severity of dementia, or Apo-E genotype. CSF total tau has diagnostic limitations, because it is increased in other disorders. Increased CSF levels of total tau may occur in patients with neurological disease that are not germane to the differential diagnosis of AD (e.g. encephalitis, Guillain-Barre syndrome, or amyotrophic lateral sclerosis [ALS]). The only conditions besides AD in which CSF tau is consistently increased are Creutzfeld-Jakob disease, encephalitis, brain trauma, and acute stroke.

This suggests that increased CSF tau levels reflect rats or neuronal or axonal degeneration or destruction. About 20-40% of patients with non-AD dementias such as vascular dementia and fronto-temporal dementia have increased CSF levels. Thus increased total tau is not specific for AD, but may occur in degenerative conditions with tau pathology or in rapidly progressive disorders (Galasko, 2001).

12. While general guidance is provided regarding determining the levels of phosphorylated tau from CSF samples taken from leukemia patients, no working examples are provided re: a broad survey of the phosphorylated tau levels in normal or unaffiliated patients, determining tau levels independent of phosphorylation, of non-ELISA methods of determining phosphorylated tau levels, or any *in vivo* methods of determining tau levels, phosphorylated or not.

13. Thus the claimed invention is directed to an *in vitro* method for early detection and/or quantification of CNS damage in an individual, which is not supported by the teachings of the specification or the prior art. One skilled in this art would be expected to reasonably doubt that the claimed method would work due to the following obstacles: Specificity of tau levels in association with any given neurological ailment or injury; How would the a spinal tap (to remove CSF for assay) affect the patients; Are tau levels specific enough to warrant a specific course of treatment?; Expectation of success in finding "elevated" tau levels when all examples in the specification show a wide range of tau levels; Expectation of success in differentiating the myriad of causes that lead to elevated tau levels in CSF. The specification does not provide guidance on how to overcome expected obstacles. The scope of patent protection sought by Applicant as defined by the claims fails to correlate reasonably with the scope of enabling disclosure provided by the specification and prior art for the following reasons.

14. Regarding CNS damage, the art recognizes that "CNS damage" pertains to trauma, cancer, tumors, poisonings, injury, disease, both by infectious agents and genetic, and disorders. Due to the large quantity of experimentation necessary to all the applicable forms of CNS damage, the lack of direction/guidance presented in the specification regarding evaluating tau levels in all applicable embodiments of CNS damage, the absence of working examples directed to known applicable forms of CNS damage, the complex nature of the invention, the unpredictability of the effects of CNS damage (Stedman's Medical Dictionary; Pilkington et al., 1997; Arvanitakis and Wszolek, 2001; Kapaki et al., 2000; Bitsch et al., 2002; Spillantini and Goedert, 1998; Molina et al., 1997; Ellis et al., 1998; Thompson and Bertram, 2001; von Zallinger and Tempel, 1998; Walsh, 1996; Dengler et al., 1998; Zhang and Tuomanen, 1999; Qureshi et al., 1998), and the breadth of the claims which fail to recite limitations for what constitutes applicable CNS damage, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

15. Regarding tumors, the art recognizes that "tumor" pertains any cell is cancerous. Due to the large quantity of experimentation necessary to all the applicable tumors, the lack of direction/guidance presented in the specification regarding evaluating tumors in all applicable embodiments of CNS damage, the absence of working examples directed to all known applicable forms of brain tumors, the complex nature of the invention, the unpredictability of the effects of tumor growth and treatment thereof (Stedman's Medical Dictionary; Pilkington et al., 1997; von Zallinger and Tempel, 1998; Walsh, 1996), and the breadth of the claims which fail to recite limitations for what constitutes applicable brain tumors, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

16. Regarding hydrocephalus, the art recognizes that "hydrocephalus" pertains to a condition marked by an excessive accumulation of CSF resulting in dilation of the cerebral ventricles and raised intracranial pressure caused by a myriad of disease, disorders, infections, and/or trauma. Due to the large quantity of experimentation necessary to all the applicable causes and results of hydrocephalus, the lack of direction/guidance presented in the specification regarding evaluating hydrocephalus in all applicable embodiments of CNS damage, the absence of working examples directed to all known applicable forms of hydrocephalus, the complex nature of the invention, the unpredictability of the effects of hydrocephalus (Stedman's Medical Dictionary; Thompson and Bertram, 2001; von Zallinger and Tempel, 1998; Zhang and Tuomanen, 1999), and the breadth of the claims which fail to recite limitations for what constitutes hydrocephalus, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

17. Regarding hematoma (or "haematoma" as spelled in the claims), the art recognizes that "hematoma" pertains to a localized mass of extravasated blood that is relatively or completely confined within an organ or tissue, a space, or a potential space which is caused by a myriad of disease, disorders, infections, and/or trauma. Due to the large quantity of experimentation necessary to all the applicable causes and results of hematoma, the lack of direction/guidance presented in the specification regarding evaluating hematoma in all applicable embodiments of CNS damage, the absence of working examples directed to all known applicable forms of hematoma, the complex nature of the invention, the unpredictability of the effects of hematoma on patients (Stedman's Medical Dictionary; Van Gool et al., 2000), and the breadth of the claims

which fail to recite limitations for what constitutes hematoma, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

18. Regarding parasites, the art recognizes that "parasite" pertains any organism that lives in a parasitic relationship with its host. Due to the large quantity of experimentation necessary to all the applicable parasites, the lack of direction/guidance presented in the specification regarding evaluating parasites and their roles in all applicable embodiments of CNS damage, the absence of working examples directed to all known applicable CNS parasites, the complex nature of the invention, the unpredictability of the effects of parasitic infection upon the CNS (Stedman's Medical Dictionary; Michael, 2002; Ellis et al., 1998; Thompson and Bertram, 2001; Dengler et al., 1998; Zhang and Tuomanen, 1999; Qureshi et al., 1998), and the breadth of the claims which fail to recite limitations for what constitutes an applicable parasite, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

19. Regarding invasion, the art recognizes that "invasion" pertains any entrance of a foreign object, organism, or agent into the CNS. Due to the large quantity of experimentation necessary to all the applicable "invasion of the CNS", the lack of direction/guidance presented in the specification regarding evaluating "invasion of the CNS" and their roles in all applicable embodiments of CNS damage, the absence of working examples directed to all known applicable instances of the "invasion of the CNS", the complex nature of the invention, the unpredictability of the effects of "invasion of the CNS" (Stedman's Medical Dictionary; Ellis et al., 1998; Thompson and Bertram, 2001; Pilkington et al., 1997; Walsh, 1996; Zhang and Tuomanen, 1999; Qureshi et al., 1998), and the breadth of the claims which fail to recite limitations for what

constitutes "invasion of the CNS", undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

20. Regarding metastasis, the art recognizes that "metastasis" pertains any tumor cell which has spread from its point of origin to a new site. Due to the large quantity of experimentation necessary to all the applicable tumor metastasis, the lack of direction/guidance presented in the specification regarding evaluating tumor metastasis in all applicable embodiments of CNS damage, the absence of working examples directed to all known applicable forms of brain metastasis, the complex nature of the invention, the unpredictability of the effects of tumor metastasis (Stedman's Medical Dictionary; Pilkington et al., 1997; von Zallinger and Tempel, 1998; Walsh, 1996), and the breadth of the claims which fail to recite limitations for what constitutes brain metastasis, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

21. Regarding organisms, the art recognizes that "organism" pertains any living being, plant or animal. Due to the large quantity of experimentation necessary to all the applicable organisms, the lack of direction/guidance presented in the specification regarding evaluating all known and unknown organisms and their roles in all applicable embodiments of CNS damage, the absence of working examples directed to all known applicable CNS associated organisms, the complex nature of the invention, the unpredictability of the effects of organisms upon the CNS (Stedman's Medical Dictionary; Michael, 2002; Ellis et al., 1998; Thompson and Bertram, 2001; Dengler et al., 1998; Zhang and Tuomanen, 1999; Qureshi et al., 1998), and the breadth of the claims which fail to recite limitations for what constitutes applicable organisms, undue

experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

22. Regarding anoxia, the art recognizes that "anoxia" pertains to the absence or almost complete absence of oxygen from inspired gases, arterial blood, or tissues which is caused by a myriad of disease, disorders, infections, and/or trauma. Due to the large quantity of experimentation necessary to all the applicable causes and results of anoxia, the lack of direction/guidance presented in the specification regarding evaluating anoxia in all applicable embodiments of CNS damage, the absence of working examples directed to all known applicable forms of anoxia, the complex nature of the invention, the unpredictability of the effects of anoxia on patients (Stedman's Medical Dictionary; Bitsch et al., 2002), and the breadth of the claims which fail to recite limitations for what constitutes anoxia, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

23. Regarding ischemia, the art recognizes that "ischemia" pertains any instance of inadequate blood circulation due to a mechanical obstruction in the circulatory system. Due to the large quantity of experimentation necessary to all the applicable causes of ischemia, the lack of direction/guidance presented in the specification regarding evaluating all known and unknown instances and degrees of severity of ischemia in all applicable embodiments of CNS damage, the absence of working examples directed to all known applicable CNS associated damage due to or involving ischemia, the complex nature of the invention, the unpredictability of the effects of ischemia upon the CNS (Stedman's Medical Dictionary; Bitsch et al., 2002; Thompson and Bertram, 2001), and the breadth of the claims which fail to recite limitations for what constitutes

applicable instances or causes of ischemia, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

24. Regarding agents, the art recognizes that "agents" can pertains compound, substance, inanimate or animate object, beings, active force, whether known or unknown, toxins, poisons, proteins, nucleic acids, organisms, parasites, chemicals, acts of nature, both inorganic and organic, energy, such as radiation, UV, or nuclear, and any object or being, known or unknown, capable of acting upon or being used to act upon as a tool or device, on the patient in question. Due to the large quantity of experimentation necessary to all the applicable agents, the lack of direction/guidance presented in the specification regarding evaluating all applicable agents capable of causing CNS damage, the absence of working examples directed to all known applicable forms of agents, the complex nature of the invention, the unpredictability of the effects of agents on CNS damage (Stedman's Medical Dictionary; Ellis et al., 1998; Van Gool et al., 2000; Thompson and Bertram, 2001; von Zallinger and Tempel, 1998; Zhang and Tuomanen, 1999; Qureshi et al., 1998), and the breadth of the claims which fail to recite limitations for what constitutes an applicable agent, physical or chemical, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

25. Regarding viral or bacterial encephalitis, the art recognizes that "encephalitis" pertains to an inflammation of the brain due to viral or bacterial infection. Due to the large quantity of experimentation necessary to all the applicable pathogenic encephalitis causing viruses and bacteria, the lack of direction/guidance presented in the specification regarding evaluating pathogenic encephalitis causing viruses and bacteria and their roles in all applicable embodiments of CNS damage, the absence of working examples directed to all known applicable

instances of pathogenic encephalitis causing viruses and bacteria, the complex nature of the invention, the unpredictability of the effects pathogenic encephalitis causing viruses and bacteria (Stedman's Medical Dictionary; Sussmuth et al., 2001; Michael, 2002; Ellis et al., 1998; Thompson and Bertram, 2001; Zhang and Tuomanen, 1999; Qureshi et al., 1998), and the breadth of the claims which fail to recite limitations for what constitutes viral or bacterial encephalitis undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

26. Regarding viral or bacterial meningitis, the art recognizes that "meningitis" pertains to an inflammation of the membranes of the brain or spinal cord due to viral or bacterial infection. Due to the large quantity of experimentation necessary to all the applicable pathogenic meningitis causing viruses and bacteria, the lack of direction/guidance presented in the specification regarding evaluating pathogenic meningitis causing viruses and bacteria and their roles in all applicable embodiments of CNS damage, the absence of working examples directed to all known applicable instances of pathogenic meningitis causing viruses and bacteria, the complex nature of the invention, the unpredictability of the effects pathogenic meningitis causing viruses and bacteria on tau levels in patients (Stedman's Medical Dictionary; Michael, 2002; Sussmuth et al., 2001; Thompson and Bertram, 2001; Dengler et al., 1998; Zhang and Tuomanen, 1999; Qureshi et al., 1998), and the breadth of the claims which fail to recite limitations for what constitutes viral or bacterial meningitis undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

27. Regarding stroke, the art recognizes that "stroke" pertains to any acute clinical event, related to impairment of cerebral circulation, that lasts more than 24 hours. Due to the large

quantity of experimentation necessary to all the applicable causes of stroke, the lack of direction/guidance presented in the specification regarding evaluating stroke in all applicable embodiments of CNS damage, the absence of working examples directed to all known applicable instances of stroke, the complex nature of the invention, the unpredictability of the effects stroke (Stedman's Medical Dictionary; Bitsch et al., 2002; Thompson and Bertram, 2001), and the breadth of the claims which fail to recite limitations for what constitutes stroke undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

28. Regarding pharmaceuticals, the art recognizes that "pharmaceuticals" or more narrowly, substances prepared for therapeutic use, can pertain to chemical entities, pharmaceutical compositions, proteins, peptides, non-peptide compounds, animal tissue extracts, vegetable extracts, cell extracts, synthetic agents, biologically derived substances as well as proteinaceous substances, known, and unknown compounds. Due to the large quantity of experimentation necessary to all the applicable pharmaceuticals, the lack of direction/guidance presented in the specification regarding synthesizing, screening, and evaluating all applicable pharmaceutically active compounds, the absence of working examples directed to known pharmaceuticals, the complex nature of the invention, the unpredictability of the effects of pharmaceuticals compositions on cells (Stedman's Medical Dictionary; Van Gool et al., 2000), and the breadth of the claims which fail to recite limitations for what constitutes an applicable pharmaceutical composition, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

29. Regarding chemotherapy, the art recognizes that "chemotherapy" pertains to the treatment of disease by means of chemical substances or drugs. Due to the large quantity of experimentation necessary to all the applicable forms, regiments, and substances used in chemotherapy, the lack of direction/guidance presented in the specification regarding synthesizing, screening, and evaluating all applicable chemotherapy agents, the absence of working examples directed to known chemotherapy regiments, the complex nature of the invention, the unpredictability of the effects of chemotherapy (Stedman's Medical Dictionary; Pilkington et al., 1997), and the breadth of the claims which fail to recite limitations for what constitutes chemotherapy, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

30. Regarding radiation, the art recognizes that "radiation" pertains to most forms of energy, but usually nuclear in reference to biology and medicine (e.g. X-rays, gamma-rays, α- and β-particles). Due to the large quantity of experimentation necessary to all the applicable forms of radiation, the lack of direction/guidance presented in the specification regarding evaluating all applicable forms of radiation, the absence of working examples directed to known biologically-relevant forms of radiation, the complex nature of the invention, the unpredictability of the effects of radiation (Stedman's Medical Dictionary; von Zallinger and Tempel, 1998), and the breadth of the claims which fail to recite limitations for what constitutes radiation, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

31. Regarding treatment, the art recognizes that "treatment" pertains a myriad of regiments, actions, pharmaceuticals, and therapies involved in the medical management of a patient. Due to

the large quantity of experimentation necessary to all the applicable forms of treatment, the lack of direction/guidance presented in the specification regarding evaluating all applicable forms of treatment, the absence of working examples directed to CNS treatments, the complex nature of the invention, the unpredictability of treatment (Stedman's Medical Dictionary; Arvanitakis and Wszolek, 2001; Van Gool et al., 2000; Michael, 2002; Bitsch et al., 2002; von Zallinger and Tempel, 1998; Dengler et al., 1998), and the breadth of the claims which fail to recite limitations for what constitutes treatment, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

32. Finally, the application must establish a nexus between the tau levels recited in the claims for each form of CNS damage and a measurable, significant change in tau levels recited in the claims. In this case, the skilled artisan is not guided as to how any given form of CNS damage must affect one or more activates of the brain or spinal cord such that the tau level change would be determined to be one that is associated with said CNS damage. Also, the tau levels cited in the specification are varied and it is not clear that tau levels would be sufficiently involved in a rate-limiting step for any form of CNS damage such that it could be used in a to evaluate the state or condition of a specific form of CNS damage to warrant a specific treatment thereby providing relief from said CNS damage. Also, the tau as measured in the patients was phosphorylated not absolute levels of tau in the spinal cord and not the brain *per se*. In addition, tau appears to be elevated in a broad range of neurological traumas and not necessarily associated with any particular stage of the trauma, disease, or disorder, whether early or not (Arvanitakis and Wszolek, 2001; Kapaki et al., 2000; Spillantini and Goedert, 1998; Molina et al., 1997; Ellis et

al., 1998; Bitsch et al., 2002; Sussmuth et al., 2001; Galasko, 2001; Thompson and Bertram, 2001; Pilkington et al., 1997; Dengler et al., 1998; Zhang and Tuomanen, 1999).

33. Claims 1-3 and 5-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims do not recite what result is required to achieve the goals set forth in the preambles. Thus the claims are incomplete.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

34. Claims 1, 2, and 3 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5601985 (Troganowski et al.) US 5601985 teaches a method of detecting tau levels in the cerebrospinal fluid of patients. US 5601985 teaches a method of detecting tau levels in cerebrospinal fluid using a monoclonal antibody thus meeting the limitations of claims 2 and 3 (Claims 1-4). US 5601985 also describes a method of detecting the level of tau in the cerebrospinal fluid of AD patients, patients with non-AD neurological disease, and normal patients using an ELISA assay thus meeting the limitations of claims 1, 2, and 3 (FIG 4; Col. 7 lines 55-67, Col. 8 lines 1-21). The phrase "for the early detection..." is an intended use and is not afforded patentable weight in accordance with case law. US 5601985 teaches the method steps (1) determining the level of tau in an individual with the recited CNS damage, (2)

comparing it to the level of tau in control healthy individuals. Since US 5601985 discloses the method steps it is fully anticipatory. Thus US 5601985 anticipates claims 1, 2, and 3.

Summary

35. Claims 1-3 and 5-11 are hereby rejected.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher Nichols, Ph.D. whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:30AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, Ph.D. can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

CJN
December 16th, 2002

ELIZABETH KEMMERER
PRIMARY EXAMINER